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Invited speaker at Joint BSI NVVI Congress, Liverpool, UK. 6-9 December 2016
<http://bsicongress.com/>

Friday, 9 December 2016: 9.00-11.00

Session: A ONE-HEALTH perspective: Novel TB vaccines and biomarkers for humans and animals

Multi-stage subunit vaccine development against *Mycobacterium paratuberculosis* and Johne's disease in ruminants

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Mycobacterium avium subsp. *paratuberculosis* (*Map*) is the causal agent of paratuberculosis or Johne's disease (JD) in ruminants. JD mainly affects the small intestine and the GALT, but is otherwise a typical mycobacterial disease with granulomatous inflammation and slow *Map* replication in macrophages. The disease progression is very slow with neonatal animals being the most susceptible to infection, but without development of detectable IFN- γ responses for months after infection and rarely with clinical disease before the second or third year of life. Available whole cell vaccines against paratuberculosis provide only partial protection and interfere with diagnostic tests for JD and surveillance for bovine TB. In contrast, recombinant subunit vaccines can be designed to be used without compromising control of bTB and *Map*.

Taking advantage of data from mouse TB studies, and early *Map* vaccination- and field-studies we developed a vaccine with a single recombinant fusion protein comprising four acute-stage antigens (Ags) and one latent-stage Ag formulated in adjuvant (FET-vaccine). In post-exposure vaccination of calves and goats with necropsy 8-12 months post inoculation, we determined that vaccination at an immunocompetent age 4 months after neonatal inoculation provided better protection than early vaccination at the time of inoculation. In pre-exposure vaccination of young calves 2-11 weeks of age followed by high-dose *Map* challenge, the observed protection was variable, without any correlation with age and less protective than animals vaccinated with killed whole-cell *Map* vaccine. Short-term studies with killing 9 weeks post challenge failed to show any protective effect of vaccination, while some animals were protected in longer studies with killing 28 weeks post inoculation. Collectively, these results indicate that induction of protective cell-mediated immunity to *Map* is more dependent on immunocompetence at time of vaccination than early vaccination, and that vaccine efficacy can only reliably be evaluated in long-term studies.

It is a common perception that vaccines against mycobacterial infections should induce Th1 responses, characterized by Ag-specific IFN- γ and possibly polyfunctional CD4⁺ T cells, to provide sustained protection. This is in line with our early observations of a reduced IFN- γ response to vaccination in neonates compared to the better protected older calves, but in vaccination-challenge studies protection was not associated with level of FET-specific IFN- γ production, and *Map*-specific IFN- γ production appeared as a surrogate of disease with an inverse relationship to level of *Map* in tissues at slaughter. Polyfunctional T cells were induced by FET vaccination, but could not be sustained during the long-term infection although FET- and *Map*-specific IFN- γ levels increased throughout the study period.